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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WALKER & JOCKE, L.P.A.
231 SOUTH BROADWAY STREET
MEDINA, OH 44256

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,269	PEREZ RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-20* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 12-14* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 6/2/2007 has been received and entered into the application file. Claim 9 has been amended; claims 10 and 11 have been cancelled; no new claims have been added. All arguments have been fully considered, and will each be addressed below, as appropriate. Rejections/objections not repeated below have been withdrawn.

Claims 1-9 and 12-20 remain pending in the current application; claims 9 and 12-14 have been considered on the merits.

Election/Restrictions

Claims 1-8 and 15-20 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/14/2007.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 371, which papers have been placed of record in the file. The instant application is a national stage entry of PCT/CU03/00012, filed 22 October 2003, which claims foreign priority to Cuban national application 239/2002 filed on 23 October 2002. A certified copy of the Cuban national application (in the Spanish language) has been received and entered into the application file.

Abstract

The amendments to the abstract, submitted 6/2/2007 are accepted. The amended abstract complies with MPEP § 608.01(b).

Claim Objections

Claim 9 is objected to because of the following informalities:

The amendment to claim 9 introduces a Roman numeral system, which uses "**I.**" and "**II.**" This system is objected to because a claim can technically only contain one period ("."); it would be remedial to replace the periods after Roman numeral I and II with brackets or parenthesis.

Furthermore, it is noted that the sub-steps of the second stage begin with step **vii**, instead of **i**. The steps should be **i - ix**, not **vii - xvi**. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Keen et al (Cytotechnology, 1996).

Applicants' amended claims are directed to a mammalian NS0 cell line adapted to growth in a serum- and protein-free media. Dependent claims require the NS0 cells to contain sequences encoding for recombinant polypeptides or proteins, more specifically recombinant antibodies or fragments thereof. The claims are determined to be product-by-process claims, the process limitations being directed to an adaptation method for adapting the cells to protein-free conditions. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, unless the method of production imparts a unique structural feature to the product. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ

964, 966 (Fed. Cir. 1985). In the instant case the method of adaptation to survival protein-free culture does not affect the cell line, per se, as the method does not impart any patentable distinctions to the cell line. Therefore, any mammalian NS0 cell line adapted to growth in serum- and protein-free media, with the claimed characteristics, anticipates the claims.

Keen et al disclose GS-engineered NS0 cell lines adapted to grow in serum-free and protein-free media (See Keen et al, abstract). Keen et al culture NS0 9D4.5A 11 (9D4) cells, NS0 2H5 cells (2H5), and NS0 8C9.50B5 (8C9) cells; 9D4 and 2H5 cells express CAMPATH-1H antibodies, and 8C9 cells express humanized anti-CD2 antibody (See Keen et al, Pg. 209, col. 1 and Pg 210, col. 2-Pg. 212, col. 2). Each of the cell lines therefore contain sequences encoding for recombinant antibodies.

Applicant's Response

Applicants have asserted that the cell line disclosed by Keen et al require supplementation with insulin, cholesterol and lipids, and thus the cells of Keen et al are metabolically distinct from the cells of the current claims, which are adapted to grow in serum and protein-free media completely without supplements.

Applicants' arguments are not found persuasive for two reasons:

First, it is respectfully submitted that the statement "[T]he presently claimed cell line grows in a protein and serum free media completely without supplements" is arguing limitations not in the presently examined claims. The current claims do require the NS0 cells to be adapted to growth in a serum- and protein-free media, but the current claims do not exclude any other supplements.

Second, based on the fact that the current claims do not exclude *any* supplements, but only protein, Applicants' argument that the cells of Keen et al require supplementation with insulin, cholesterol and lipids is only relevant with regards to insulin (as neither cholesterol or lipids are proteins). However, it is respectfully submitted that Applicants are relying on a single embodiment of Keen et al, wherein

Keen et al noted the addition of 5 mg/L of Nucellin (human recombinant insulin) *slightly increased* the growth rate of 9D4, 2H5 and 8C9 cells in the serum- and protein-free WNSA + lipids media (See paragraph spanning col. 1-2 of Pg. 212 of Keen et al); however Keen et al do not report insulin as necessary for cell growth, as evidenced by Fig. 1. Figure 1 compares cell growth in WNSA protein-free media, supplemented with *either* 1. lipid, beta-cyclodextrin and recombinant insulin, 2. lipids with extra ribonucleotide; 3. lipids with extra glutamic acid and asparagine; or 4. lipids with extra glutamic acid, asparagine, and ribonucleosides. Highest cell growth and antibody production was achieved with medium 4- which does not contain insulin or other proteins. (See PG. 213, col. 1 and Fig. 1). Therefore, each of the NS0 9D4, 2H5 and 8C9 cells were capable of growing in completely serum- and protein-free media, and thus meet the limitations of the instant claims. Thus the rejection under 35 USC 102(b) based on Keen et al is maintained as appropriate.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keen et al (Cytotechnology, 1996), in view of Crombet-Ramos et al (Int. J. Cancer, 2002, published online 27 August 2002).

Applicants' amended claims are directed to a mammalian NS0 cell line adapted to growth in a serum- and protein-free media. Dependent claims require the NS0 cells to contain sequences encoding for recombinant polypeptides or proteins, more specifically recombinant antibodies or fragments thereof, and more specifically the humanized recombinant antibody anti-EGF-R hR3 or a fragment thereof. The

claims are determined to be product-by-process claims, the process limitations being directed to an adaptation method for adapting the cells to protein-free conditions. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, unless the method of production imparts a unique structural feature to the product. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case the method of adaptation to survival protein-free culture does not affect the cell line, per se, as the method does not impart any patentable distinctions to the cell line. Therefore, any mammalian NS0 cell line adapted to growth in serum- and protein-free media, with the claimed characteristics, anticipates the claims.

Keen et al disclose NS0 cell lines which are adapted to grow in serum- and protein-free media (See Keen et al, abstract). Keen et al states that production of antibodies and therapeutic proteins in fully defined (serum- and protein-free) media is desirable due to lower cost, better reproducibility, regulatory considerations and purification of the product (See Keen et al, Pg. 208, third full paragraph). Keen et al disclose NS0 9D4.5A 11 (9D4) cells, NS0 2H5 cells (2H5), and NS0 8C9.50B5 (8C9) cells; 9D4 and 2H5 cells express CAMPATH-1H antibodies, and 8C9 cells express humanized anti-CD2 antibody (See Keen et al, Pg. 209, col. 1 and Pg 210, col. 2-Pg. 212, col. 2). Keen et al do not disclose NS0 cells which product a humanized anti-EGFR antibody hR3.

At the time the invention was made, the humanized anti-EGFR antibody hR3 was recognized as a potential anti-cancer agent (See Crombet-Ramos et al, abstract), and thus production of this antibody was desirable.

Because production of humanized anti-EGFR antibody hR3 was recognized as desirable, it would thus have been obvious to one of ordinary skill in the art to use the method of Keen et al to create NS0 cells engineered to produce humanized anti-EGFR antibody hR3, wherein the cells are adapted to grow in serum- and protein-free media.

One would have had a reasonable expectation of successfully engineering the NS0 cells to encode for the anti-EGFR antibody hR3 because the coding sequence for the anti-EGFR antibody hR3 was known in the art (See Crombet-Ramos et al), and because methods of engineering NS0 cells to encode for any desired sequence, as well as methods of adapting NS0 cells to growth in serum- and protein-free conditions were known in the art (See Keen et al). Thus, it would have been within the technical grasp of the artisan of ordinary skill to transduce NS0 cells to encode for the anti-EGFR antibody hR3 coding sequence, and then to subject those cells to the method of Keen et al, wherein the cells are adapted to serum- and protein-free growth to produce the transduced protein sequence. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants' Response

Applicants have asserted the Office has not established a *prima facie* case of obviousness because Keen et al does not disclose each and every limitation of the current claims, and the secondary references do no remedy this deficiency.

In response, the arguments as to Keen et al have been addressed above. Keen et al is maintained as an appropriate grounds of rejection. Absent specific arguments as to the combination of references as they relate to the subject matter of claim 14, the rejection under 35 USC 103(a) is also maintained as appropriate.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651